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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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10/813,467

03/29/2004

Bill J. Peck

10031551-1

4799

22878 7590 12/29/2008

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INTELLECTUAL PROPERTY ADMINISTRATION,LEGAL DEPT.  
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EXAMINER

CROW, ROBERT THOMAS

ART UNIT

PAPER NUMBER

1634

NOTIFICATION DATE

DELIVERY MODE

12/29/2008

ELECTRONIC

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

IPOPS.LEGAL@agilent.com

<b>Advisory Action</b> <b>Before the Filing of an Appeal Brief</b>	<b>Application No.</b> 10/813,467	<b>Applicant(s)</b> PECK ET AL.	
	<b>Examiner</b> Robert T. Crow	<b>Art Unit</b> 1634	

**--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --**

THE REPLY FILED 11 December 2008 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

1. ☒ The reply was filed after a final rejection, but prior to or on the same day as filing a Notice of Appeal. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. The reply must be filed within one of the following time periods:

- a) ☐ The period for reply expires \_\_\_\_\_ months from the mailing date of the final rejection.  
 b) ☒ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.

Examiner Note: If box 1 is checked, check either box (a) or (b). ONLY CHECK BOX (b) WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

#### NOTICE OF APPEAL

2. ☐ The Notice of Appeal was filed on \_\_\_\_\_. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

#### AMENDMENTS

3. ☒ The proposed amendment(s) filed after a final rejection, but prior to the date of filing a brief, will not be entered because  
 (a) ☐ They raise new issues that would require further consideration and/or search (see NOTE below);  
 (b) ☐ They raise the issue of new matter (see NOTE below);  
 (c) ☒ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or  
 (d) ☐ They present additional claims without canceling a corresponding number of finally rejected claims.

NOTE: The amendment is non-compliant, and thus does not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal. (See 37 CFR 1.116 and 41.33(a)).

4. ☒ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).  
 5. ☐ Applicant's reply has overcome the following rejection(s): \_\_\_\_\_.  
 6. ☐ Newly proposed or amended claim(s) \_\_\_\_\_ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).  
 7. ☒ For purposes of appeal, the proposed amendment(s): a) ☒ will not be entered, or b) ☐ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.  
 The status of the claim(s) is (or will be) as follows:  
 Claim(s) allowed: None.  
 Claim(s) objected to: None.  
 Claim(s) rejected: 28-59 and 61.  
 Claim(s) withdrawn from consideration: None.

#### AFFIDAVIT OR OTHER EVIDENCE

8. ☐ The affidavit or other evidence filed after a final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).  
 9. ☐ The affidavit or other evidence filed after the date of filing a Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing a good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).  
 10. ☐ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

#### REQUEST FOR RECONSIDERATION/OTHER

11. ☒ The request for reconsideration has been considered but does NOT place the application in condition for allowance because:  
See Continuation Sheet.  
 12. ☐ Note the attached Information *Disclosure Statement*(s). (PTO/SB/08) Paper No(s). \_\_\_\_\_.  
 13. ☐ Other: \_\_\_\_\_.

/Ram R. Shukla/  
 Supervisory Patent Examiner, Art Unit 1634

Continuation of 11. does NOT place the application in condition for allowance because:

A. Applicant argues on page 9 of the Remarks filed 11 December 2008 (hereafter the "Remarks") that Gamble does not teach wash reagents contacting the entire surface of the substrate. Thus, Applicant is attacking the individual reference of Gamble et al.

However, as noted in the previous Final Office Action, Gamble et al merely lack the teaching that the wash solution flows through the same chamber even though Gamble et al explicitly teach the substrate is placed in a reaction chamber wherein reagents flow over and immerse the substrate (column 3, line 45-column 4, line 5), and that the reagents include phosphoramidites (i.e., blocked nucleoside monomers), wash reagents, deprotection (i.e. deblocking) reagents, activation reagents, oxidation reagents, and any other necessary synthesis reagents (column 4, lines 35-46).

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

B. Applicant argues on page 9 of the Remarks that Anderson et al do not teach in situ fabrication of an array. Thus, Applicant is attacking the individual reference of Gamble et al.

However, as noted in the previous Final Office Action, Anderson et al is not relied upon for the teaching of the formation of an in situ array. Anderson et al clearly teach in situ synthesis of oligonucleotides on a substrate, and further teach the forming of a liquid-liquid interface such that the solid support is not exposed to a triple phase interface (column 12, lines 28-67 and Fig. 2A-2D), as well as teaching the use of a single hollow chamber as a reaction chamber has the added advantage of allowing precise control of fluid flow and minimization of both micro-and macro-anomalous flow (Abstract).

In response to applicant's arguments against the references individually, it is reiterated that one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references.

C. Applicant argues on pages 9-10 of the Remarks that because the prior art of Gamble et al and Anderson et al are "very different methods," there is no motivation to combine the references.

In response to applicant's argument that the cited references are "very different methods" (i.e., nonanalogous art), it has been held that a prior art reference must either be in the field of applicant's endeavor or, if not, then be reasonably pertinent to the particular problem with which the applicant was concerned, in order to be relied upon as a basis for rejection of the claimed invention. See *In re Oetiker*, 977 F.2d 1443, 24 USPQ2d 1443 (Fed. Cir. 1992). In this case, Gamble et al teach a method of in situ forming of an oligonucleotide array using a flow of reagents through a flow chamber as described in the previous Final Office Action. Anderson et al teach known technique of performing all of the fluid steps, including washing, with a single reaction chamber during an in situ synthesis of oligonucleotides on a solid support as described in the previous Final Office Action. Thus, the methods bear a striking similarity, and are not, as Applicant asserts, "very different methods."

In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, Anderson et al also teach the use of a single hollow chamber as a reaction chamber has the added advantage of allowing precise control of fluid flow and minimization of both micro-and macro-anomalous flow (Abstract). Thus, Anderson et al teach the known technique of performing all of the fluid steps, including washing, with a single reaction chamber.

Thus, as clearly stated in the previous Final Office Action, it would have been obvious to a person of ordinary skill in the art at the time the claimed invention was made to have modified the method comprising steps including washing of the array substrate as taught by Gamble et al so that each previous reagent is quantitatively replaced by a washing fluid as taught by Anderson et al and so that the reaction chamber of Gamble et al is used as a single reaction chamber for all of the fluid manipulation steps as taught by Anderson et al arrive at the instantly claimed method with a reasonable expectation of success. Quantitative replacement of reagents on the surface of the support requires displacement of said reagent from the entire surface of the substrate via use of the washing fluid as taught by Anderson et al. The ordinary artisan would have been motivated to make the modification because said modification would have resulted in a method having the added advantage of ensuring that each reagent reacts properly so that the yield of the polymer is not diminished, thus meeting the fixed requirements of washing efficiency and quantitative replacement of solutions during polymer synthesis as explicitly taught by Anderson et al (column 19, lines 25-40 and column 3, lines 45-60). The ordinary artisan would also have been motivated to use the single reaction chamber of Anderson et al as a single reaction chamber for all of the fluid steps in the method of Gamble et al because the use of a single reaction chamber for all of the fluid steps, including washing, would have resulted in a method having the additional added advantage of allowing precise control of fluid flow and minimization of both micro-and macro-anomalous flow as explicitly taught by Anderson et al (Abstract). In addition, it would have been obvious to a person of ordinary skill in that art at the time the claimed invention was made that the known technique of performing all of the fluid steps, including washing, with a single reaction chamber as taught by Anderson et al could have been applied to the method of Gamble et al with predictably results because the known technique of performing all of the fluid steps, including washing, with a single reaction chamber as taught by Anderson et al predictably results in a reliable method of performing DNA synthesis steps.

In addition, it is also noted that under the Supreme Court ruling for KSR Int'l Co. v. Teleflex, Inc (No 04-1350 (US 30 April 2007) forecloses the argument that a specific teaching, suggestion, or motivation is required to support a finding of obviousness. See Ex parte Smith (USPQ2d, slip op. at 20 (Bd. Pat. App. & Interf. June 25, 2007).

D. Applicant argues on page 10 of the Remarks that Anderson et al requires a rotor, which results in a nonfunctional embodiment, and would damage the array and render in situ fabrication impossible.

However, Applicant has not provided any evidence of inoperability. As such, the argument is deemed unsupported arguments of counsel. MPEP 716.01(c) makes clear that "[t]he arguments of counsel cannot take the place of evidence in the record" (In re Schulze, 346 F.2d 600, 602, 145 USPQ 716, 718 (CCPA 1965)).

Finally, the Response above should not be construed as an invitation to file an after final declaration. See MPEP 715.09 [R-3].

Second, the teaching of Anderson is not limited to rotor/centrifuge, but also includes a "column at rest" (Abstract and Column 5, lines 29-30). Hence, the combination of Gamble et al and Anderson et al would not lead to a damaged substrate as asserted by Applicant.

E. Applicant also argues on page 10 of the Remarks that there is no support that the combination results in washing efficiency or quantitative replacement of reagents.

However, as noted in the previous Final Office Action, Anderson et al teach the desire for washing efficiency and quantitative replacement of reagents, Anderson et al also teach the use of a single hollow chamber as a reaction chamber has the added advantage of allowing precise control of fluid flow and minimization of both micro-and macro-anomalous flow (Abstract). Thus, the control of both micro-and macro-anomalous flow would increase the washing efficiency because poor flow (i.e., low washing efficiency) would be minimized via the flow control.

In addition, it is reiterated that under the Supreme Court ruling for KSR Int'l Co. v. Teleflex, Inc (No 04-1350 (US 30 April 2007) forecloses the argument that a specific teaching, suggestion, or motivation is required to support a finding of obviousness.

F. Applicant also argues that Gamble et al teach drying protocols in column 13.

However, column 14 clearly states that "other versions" of the claimed invention "are possible" and column 3 of Gamble et al clearly states that anhydrous conditions in the chamber "can be accomplished" by drying. Thus, the drying protocols are non-limiting, and Gamble et al clearly allow for other methods of guaranteeing reagent removal.

G. Applicant argues on page 11 of the Remarks that numerous other teachings around to priority dates teach the prevalence of drying steps and lack the teaching of fluid displacement.

However, the presence of other references that do not teach fluid displacement does not negate the fact that the prior art of Anderson et al teaches the known technique fluid displacement in a single chamber as well as a motivation to do so as provided in the previous rejections.

H. Applicant argues on pages 11-12 that the combination of Gamble et al and Anderson et al results in an inoperable embodiment because of the alleged need for a rotating rotor and the lacking of an addressable array in Anderson et al.

However, as noted above, Applicant has not provided any evidence of inoperability. As such, the argument is deemed unsupported arguments of counsel. MPEP 716.01(c) makes clear that "[t]he arguments of counsel cannot take the place of evidence in the record."

It is reiterated that the Response above should not be construed as an invitation to file an after final declaration. See MPEP 715.09 [R-3].

Further, as also noted above, the teaching of Anderson is not limited to rotor/centrifuge, but also includes a "column at rest" (Abstract and Column 5, lines 29-30). Hence, the combination of Gamble et al and Anderson et al would not lead to a damaged substrate as asserted by Applicant.

It is also reiterated that Applicant's arguments amount to a piecemeal analysis of the references. In response to applicant's arguments against the references individually, it is reiterated that one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references.

I. Applicant also argues on pages 12-13 of the Remarks that the "Examiner has fails [sic] to articulate a reason to modify the cited references...[w]ithout hindsight provided by the instant application...."

In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See In re McLaughlin, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

J. Applicant's arguments on page 13 of the Remarks regarding the rejection of claim 37 rely on the alleged deficiencies of Gamble et al in view of Anderson et al. These arguments are addressed above. Because the arguments regarding alleged deficiencies of Gamble et al in view of Anderson et al were not persuasive, the rejection is maintained.

K. Applicant argues on page 14 of the Remarks that because Mian et al teaches channel flow in a disc, the art of Mian et al cannot be combined with Gamble et al or Anderson et al (i.e., that Mian et al is non-analogous art).

However, Gamble et al clearly teach fluid flow through channels 160 (Figure 11) and a conduit system for transporting liquids to and from the reaction chamber (column 4). Mian et al teach the advantage that variable flow rates within the claimed range allow fluid transfer over a wide range of times scales as required by the various processes (column 12, lines 40-57). Thus, Mian et al teach the known technique of using the instantly claimed flow rates and the ordinary artisan would have been motivated to make such a modification because said modification would have resulted in a method of producing an addressable array having the added advantage of having flow rates that allow fluid transfer over a wide range of times scales as required by the various processes as explicitly taught by Mian et al (column 12, lines 40-57).

L. Applicant argues on pages 14-15 of the Remarks that because Gamble et al and Bass et al lack the stratified fluid interface. Thus, Applicant poses a piecemeal analysis of the rejection by not addressing the stratified fluid interface taught by Anderson et al.

It is reiterated that one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references.

M. Applicant argues on page 15 of the Remarks that because Anderson et al teaches a rotating rotor, there can be no teaching of the use of the flow cell of Bass et al.

However, as noted above, Anderson is not limited to rotor/centrifuge, but also includes a "column at rest" (Abstract and Column 5, lines 29-30). Thus, a column at rest is a functional equivalent of the claimed "flow cell," and the use of the functionally equivalent flow cell of Bass et al is an obvious substitution for the reasons presented in the rejection.

N. Applicant argues on page 16 of the Remarks that Farr teaches a stratified blood supernatant and thus is unrelated to array synthesis; i.e., that Farr is non-analogous art.

In response to applicant's argument that Farr is nonanalogous art, it is reiterated that it has been held that a prior art reference must either be in the field of applicant's endeavor or, if not, then be reasonably pertinent to the particular problem with which the applicant was concerned, in order to be relied upon as a basis for rejection of the claimed invention. See *In re Oetiker*, 977 F.2d 1443, 24 USPQ2d 1443 (Fed. Cir. 1992). In this case, Farr refers to manipulation of stratified fluids using a pressure gradient (column 1, lines 5-10). Anderson et al also teach stratified fluids (column 12, lines 28-67 and Fig. 2A-2D). Thus, Farr is analogous to Anderson et al.

O. Applicant also argues on page 16 of the Remarks that the examiner has misconstrued the advantage taught by Farr.

However, as noted above, the Supreme Court ruling for *KSR Int'l Co. v. Teleflex, Inc* (No 04-1350 (US 30 April 2007) forecloses the argument that a specific teaching, suggestion, or motivation is required to support a finding of obviousness. Thus, it would have been obvious to the ordinary artisan that the known technique of using the pressure gradient of Farr could have been applied to the method of Gamble et al in view of Anderson et al with predictable results because the pressure gradient of Farr predictably results in reliable method of stratifying fluids, as stated in the previous Final Office Action.

Q. Applicant's remaining arguments rely on the alleged deficiencies of Gamble et al in view of Anderson et al. These arguments are addressed above. Because the arguments regarding alleged deficiencies of Gamble et al in view of Anderson et al were not persuasive, the rejections are maintained for the reasons of record.

/Robert T. Crow/  
Examiner, Art Unit 1634.